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Template version 09/11

TXR#: 0056765

DATA EVALUATION RECORD[1]

STUDY TYPE: Reproduction and Fertility Effects Study – Rat
OPPTS 870.3800 [§83-4]; OECD 416.

PC CODE: 016331 **DP BARCODE:** D410187

TEST MATERIAL (PURITY): Momfluorothrin (95.7% a.i.)

SYNONYMS: S-1563

CITATION: Pal-Kutas, K. (2012) S-1563: Two-Generation Reproduction Toxicity Study in the Han Wistar Rat. Harlan Laboratories Ltd. Fullinsdorf, Switzerland. Harland Study #C84830, August 10, 2012. MRID 49020018. Unpublished

SPONSOR: Sumitomo Chemical Co., Ltd.

EXECUTIVE SUMMARY:

In a 2-generation reproduction study (MRID 49020018) S-1563 (95.7% a.i., batch/lot 9CM0109G) was administered to Wistar rats (24/sex/dose) in the diet at dose levels of 0, 200, 500, or 1500 ppm (equivalent to 0, 12.6, 32.1, or 95.2 mg/kg/day for P generation males, 0, 14.7, 35.5, or 106.3 mg/kg/day for P generation females).

No treatment related effects were observed on mortality, clinical signs, gross pathology, or reproductive parameters. Significant decreases in body weight were observed in F1 parents at the high-dose. Additionally, increases in hepatocellular hypertrophy observed at the high-dose were considered to be adverse as they were observed at doses consistent with those causing tumors in the carcinogenicity study.

The parental systemic LOAEL is 1500 ppm (95.2 mg/kg/day in males, and 106.3 mg/kg/day in females) based on body weight impairment and liver histopathology. The parental NOAEL is 500 ppm (32.1 mg/kg/day for males and 35.5 mg/kg/day for females).

No treatment-related effects were observed on mortality, clinical signs, gross pathology or histopathology. The decreases in spleen weights observed at the mid and high-dose levels, and decreases in pup body weights at the mid-dose level were not considered to be adverse. Significant decreases in pup body weights observed at high-dose in both generations.

1 Disclaimer: The attached Data Evaluation Record is a modified version of the Tier II Summary provided by Sumitomo Chemical Co. Ltd. Portions of this document may have been altered by the EPA reviewer.

The offspring LOAEL is 1500 ppm (95.2 mg/kg/day for males and 106.3 mg/kg/day for females), based on significantly decreased body weights in both sexes of the F1 and F2 pups. The offspring NOAEL is 500 ppm (32.1 mg/kg/day for males and 35.5 mg/kg/day for females).

Time to sexual maturation was delayed in both high-dose males and female. Slight delays in sexual male maturation times are consistent with significantly decreased body weights and it is unclear if this effect is related to body weight decrements or sexual maturation *per se*. However, delayed sexual maturation in females is considered treatment related as the effect was more pronounced and occurred in the absence of significant body weight decreases.

The reproductive LOAEL is 1500 ppm (95.2 mg/kg/day in males, and 106.3 mg/kg/day in females), based on delayed sexual maturation. The reproductive NOAEL is 500 ppm (32.1 mg/kg/day in males, 35.5 mg/kg/day in females).

***Note: PMRA does not consider the delay in sexual maturation in females as an endpoint that is relevant in establishing the NOAEL for Reproductive toxicity. The delay in vaginal opening should be captured under Offspring toxicity. Therefore, the PMRA considers the NOAEL for Reproductive toxicity to be 1500 ppm (highest dose tested). Additionally, the PMRA considers the NOAEL for Parental systemic toxicity to be as follows:**

NOAEL (♂) = 32 mg/kg bw/day, based on bw effects in P gen
NOAEL (♀) = 106 mg/kg bw/day

This study is **Acceptable/Guideline** and satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800); OECD 416 in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test Material	Momfluorothrin
Description:	Not stated
Lot/Batch:	9CM0109G
Purity:	95.7% by Certificate of Analysis
CAS#:	609346-29-4
Stability:	Expiry date 07 Sept 2011 (after completion of administration)
2. Vehicle	None. Test material was mixed directly into diet.
3. Test Animals	
Species	Rat
Strain	Wistar (HanRcc^{TM}:WIST (SPF))
Age	7 weeks at study initiation
Weight	Males 206 to 255 g, females 150 to 188 g.
Source	Harlan Laboratories, B.V, Horst, NL.
Acclimation period	7 days
Diet	Pelleted standard Kliba Nafag 3433 rodent maintenance diet (Provimi Kliba SA, Switzerland) *ad libitum*
Water	Main water was provided *ad libitum* from bottles
Housing	Makrolon type-3 cages ('Lignocel' J.Rettenmaier & Söhne GmbH & CoKG) with sterilized standard softwood bedding.
Environmental conditions	
Temperature	20 – 25°C
Humidity	16.3 – 73.2%
Air change	10 – 15 air changes per hour
Photoperiod	12 hour light / dark cycle

B. PROCEDURES AND STUDY DESIGN:

1. **Mating procedure:** 24 males and 24 females from the same test group were paired until sperm cells were observed in vaginal smears or a copulation plug was observed. A period of 14 days was allowed for mating. Males failing to copulate within this period were replaced by another male from the same group.

   All P dams were allowed to give birth and rear pups until day 21 post partum. After weaning, 24 weanlings/sex/dose were randomly selected and paired in mating cages when they were at least 13 weeks, siblings were not paired.

2. **Study schedule:** Test item administration occurred over a 70-day pre-mating period and during the mating and after mating periods in males and during the mating, gestation, and lactation periods in females for breeding of the F1 litters. Following weaning of the F1 litters

on day 21 post partum, F1 animals were selected for the next generation. Treatment was maintained on their respective diets from weaning. The test item was administered during growth of the F1 generation to adulthood (at least a 91-day pre-mating period) and also during the mating, gestation and lactation periods for breeding of the F2 litters.

3. **Animal assignment:** P animals were assigned randomly by a computer-generated algorithm according to weight to test groups as seen in Table 1.

TABLE 1. Animal assignment

Test group	Concentration in diet[a] (ppm)	Animals/group			
		P Males	P Females	F_1 Males	F_1 Females
Control	0	24	24	24	24
Low (LDT)	200	24	24	24	24
Mid (MDT)	500	24	24	24	24
High (HDT)	1500	24	24	24	24

[a] Diets were administered from (beginning of the study until sacrifice)

4. **Dose selection rationale:** The dose levels were selected based on the results of a preliminary two-generation study and a 13-week study where oral-administration of up to 3000 or 6000 ppm resulted in decreased body weight gain of males and females treated at 1000 ppm and higher. Therefore, 1500 ppm was selected as the highest dose as a treatment related decrease in body weights was expected.

5. **Dosage preparation and analysis:** Formulations were prepared every 2 to 3 weeks by mixing appropriate amounts of test substance with Kliba Nafag 3433 rodent maintenance Diet and were stored at 15-25ºC in a metal container. Prior to the start of the study, stability of the test substance was evaluated for a period of 28 days at room temperature. Homogeneity (top, middle, and bottom) was evaluated for each mixture. During the study, samples of diet mixture were analyzed at each dose level for concentration.

Results:
Homogeneity analysis (%RSD): 1.7 to 15.1

Stability analysis (% Initial): 95.9 to 113.4 (4 weeks at room temperature)

Concentration analysis (% Nominal): 81.8 to 107.9

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

C. OBSERVATIONS:

1. **Parental animals:** Animals were observed for mortality/viability twice daily. Clinical observations occurred daily, with a detailed clinical examination conducted on a weekly basis. Body weights were measured on the first day of dosing and weekly following first dose. Females were weighed on days 0, 7, 14, and 21 post coitum, and then on days 1, 4, 7, 14, and 21 post partum, and on the day of sacrifice. Food consumption was recorded with body weights. During lactation, food consumption was only recorded to day 14 post partum

for females.

2. **Litter observations:** According to the report, the following litter observations were made (see Table 2).

TABLE 2. F_1 / F_2 Litter Observations [a]

Observation	Time of observation (lactation day)				
	Day 0	Day 4	Day 7	Day 14	Day 21
Number of live pups	X	X	X	X	X
Pup weight	X	X	X	X	X
External alterations	X	X	X	X	X
Number of dead pups	X	X	X	X	X
Sex of each pup (M/F)	X	X			X
Days to sexual maturation	Observed daily				

[a] Data obtained from page 35 in the study report.

On day 4 postpartum, litters were standardized to a maximum of 8 pups/litter (4/sex/litter, as nearly as possible); excess pups were killed and discarded.

Dead pups were examined grossly for external and internal abnormalities.

3. **Postmortem observations:** All animals were sacrificed by an injection of sodium pentobarbital and examined macroscopically for any structural abnormalities or pathological changes. All animals sacrificed or found dead were subjected to a detailed macroscopic examination to establish, if possible, the cause of death. Specimens of abnormal tissue were fixed in neutral phosphate buffered 4% formaldehyde solution. For the parent animals, special attention was directed at the organs of the reproductive system. Pups killed for ethical reason and pups found dead, except those excessively cannibalized, were examined macroscopically and preserved in buffered 4% formaldehyde solution.

   a. **Parental animals:** All P and F1 adult animals selected for breeding were sacrificed when they were no longer necessary for the assessment of reproductive effects. P and F1 females were sacrificed, if possible, during diestrus stage according to the results of the estrous cycles (vaginal smears).

      Females for which no pregnancy was detected were sacrificed three weeks after the last possible mating date. Females which lost their litters were sacrificed either directly after litter loss or with the other dams after weaning.

      Gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera.

Full histopathology was performed on all of the listed organs animals in the high dose as well as control P and F1 animals. If changes were detected, then the same organs from the mid- and low-dose group were then examined. The following tissues (X) were prepared for microscopic examination and weighed (XX).

XX	Ovaries	XX	Testes
XX	Uterus/Cervix	XX	Epididymides
X	Vagina	XX	Prostate
XX	Adrenal Glands	XX	Pituitary
XX	Liver	XX	Seminal vesicles and Coagulating glands
X	Gross Lesions		

Special emphasis was placed on evaluation of the stages of spermatogenesis and histopathology of interstitial cell structure. Ovarian histopathology included quantitative evaluation of primordial follicles, growing follicles and antral follicles from 10 sections per ovary in the first 10 females of the P and F1 generations in the control and high dose groups. Corpora lutea were also counted on one section per ovary.

Sperm analysis (sperm count, motility and morphology) was performed on all males from the control and high dose groups.

b. Offspring: F1 and F2 pups were culled by random selection to yield as nearly as possible 4 males and 4 females per litter on day 4 post partum. F1 pups not selected for the F1 generation mating and the remaining F2 pups were sacrificed after weaning.

D. DATA ANALYSIS:

1. Statistical analyses: The following statistical methods were used to analyze food consumption, relative food consumption, body weight, body weight gain, reproduction data (estrous cycle, fertility indices, implantations, duration of gestation, post implantation loss, litter size, pup sex ratio, viability indices, indices of mating, gestation, birth and lactation, sexual maturation and sperm analysis), organ weights, organ/body weight ratios, organ/brain weight ratios, macroscopic and microscopic findings and quantitative ovarian histopathology: Means and standard deviations of various data were calculated. The Dunnett-test (many to one t-test) based on a pooled variance estimate was applied if the variables could be assumed to follow a normal distribution for the comparison of the treated groups and the control groups for each sex. The Steel-test (many-one rank test) was applied instead of the Dunnett-test when the data could not be assumed to follow a normal distribution. Fisher's exact-test was applied if the variables could be dichotomized without loss of information. The Wilcoxon test was applied to evaluate quantitative ovarian histopathology.

2. Indices:

Reproductive indices: The following reproductive indices were calculated from breeding and parturition records of animals in the study: fertility, conception, and gestation.

Percentage mating = (Females mated / Females paired) * 100
Fertility index = (Females achieving a pregnancy / Females paired) * 100

Conception rate = (Females achieving a pregnancy / Females mated) * 100
Gestation index = (Number of females with living pups / Number of females pregnant) * 100

Offspring viability indices: The following viability indices were calculated from lactation records of litters in the study: birth, viability, and weaning.

Birth index = (number of pups born alive / number of implantations) * 100
Viability index = (number of alive pups on day 4 p.p. / number of pups born alive) * 100
Weaning index = (number of alive pups on day 21 p.p. / number of alive pups on day 4 p.p.) * 100

3. **Historical control data:** Historical control data were provided for estrous cycles, reproductive measures, and organ weights.

II. RESULTS:

A. PARENTAL ANIMALS:

1. **Mortality and clinical signs:** No mortality was observed throughout the study period. No treatment-related clinical signs were observed during daily or detailed weekly observations. Findings were limited to isolated effects and exhibited no dose-response relationship.

2. **Body weight and food consumption:** No significant differences in bodyweight were recorded for females in the P generation at any time point. Males had slight, but significantly decreased body weights during pre-mating and day 1 after mating. However, as these differences were less than 10% when compared to controls they were not considered to be biologically relevant. Significant decreases in body weight of F1 males and females were observed at the high-dose.

In parental animals, food consumption was significantly decreased at intervals during the pre-mating period at the high-dose for both sexes, and in the mid-dose for females only. Food consumption remained decreased for high-dose males post-mating. In females, food consumption was decreased between gestation days 0 and 14 at the mid-and high-dose. No effect on food consumption was observed during the lactation period in any dose group.

TABLE 4. Mean (±SD) Selected body weights P Generation[a]

Observations/study week	Dose group (ppm)			
	Control	200	500	1500
P Generation males - Pre-mating				
Mean body weight (g)				
Day 1	231 ± 10.4	227 ± 10.7	232 ± 11.5	228 ± 9.5
Day 8	282 ± 14.4	273 ± 12.6	281 ± 14.7	270 ± 12.1** (-4.3%)
Day 36	388 ± 26.0	375 ± 25.5	386 ± 28.0	362 ± 26.0** (-6.8%)
Day 70	451 ± 31.2	439 ± 32.9	453 ± 34.5	422 ± 30.6** (-6.4%)
Mean weight gain (%)				
Days 1-8	22 ± 2.6	20 ± 2.1*	21 ± 2.0	19 ± 2.3** (-13.6%)
Days 1-36	67 ± 7.6	65 ± 8.7	66 ± 7.7	59 ± 7.8** (-12%)

Observations/study week	Dose group (ppm)			
	Control	200	500	1500
Days 1-70	95 ± 9.6	93 ± 12.2	95 ± 10.1	85 ± 8.9** (-10.5%)
P Generation males – after mating				
Mean body weight (g)				
Day 1	466 ± 28.8	450 ± 30.8	466 ± 34.3	439 ± 33.4* (-5.8%)
Day 22	487 ± 31.5	474 ± 33.0	493 ± 36.3	464 ± 33.2
Day 37	491 ± 34.1	475 ± 34.7	506 ± 40.0	479 ± 29.7
Mean weight gain (%)				
Days 1-37	7 ± 2.2	8 ± 2.1	8 ± 2.4	7 ± 1.5
P Generation females - pre-mating				
Mean body weight (g)				
Day 1	167 ± 7.3	167 ± 8.8	167 ± 6.1	168 ± 6.4
Day 8	187 ± 9.1	186 ± 10.3	185 ± 5.7	184 ± 8.6
Day 36	224 ± 12.4	224 ± 13.9	221 ± 10.0	219 ± 13.4
Day 70	248 ± 14.6	248 ± 15.7	247 ± 14.2	241 ± 14.7
Mean weight gain (%)				
Days 1-8	12 ± 2.8	12 ± 2.5	11 ± 2.1	10 ± 3.2* (-16.7%)
Days 1-36	34 ± 4.7	35 ± 4.7	33 ± 3.9	30 ± 6.2
Days 1-70	48 ± 6.3	49 ± 6.1	48 ± 6.0	44 ± 8.0* (-8.3%)
P Generation females – gestation period				
Mean body weight (g)				
Day 7	271 ± 15.5	269 ± 15.9	266 ± 13.9	263 ± 16.5
Day 14	292 ± 16.3	290 ± 15.9	288 ± 14.6	284 ± 17.3
Day 21	368 ± 21.3	363 ± 18.4	363 ± 18.4	355 ± 23.1
Mean weight gain (%)				
Day 1-21	49 ± 4.9	49 ± 6.5	48 ± 4.9	48 ± 6.5
P Generation females – lactation period				
Mean body weight (g)				
Day 4	285 ± 18.2	285 ± 16.0	281 ± 11.6	284 ± 21.2
Day 7	293 ± 16.5	292 ± 14.1	288 ± 10.7	288 ± 19.6
Day 14	304 ± 15.0	301 ± 15.1	299 ± 10.4	298 ± 19.2
Day 21	292 ± 17.5	291 ± 17.3	291 ± 11.7	291 ± 17.3
Mean weight gain (%)				
Day 1-21	7 ± 5.1	8 ± 5.9	9 ± 5.9	8 ± 5.4

[a] Data obtained from pages 178-187 in the study report.
* Statistically different from control, $p<0.05$.
** Statistically different from control, $p<0.01$.

TABLE 5. Mean (±SD) Selected body weights F1 parents [a]

Observations/study week	Dose group (ppm)			
	Control	200	500	1500
F1 Generation males - Pre-mating				
Mean body weight (g)				
Day 1	169 ± 10.7	164 ± 17.2	158 ± 12.4	141 ± 20.0** (-16.6%)
Day 8	217 ± 13.8	208 ± 20.9	203 ± 14.7* (-6.5%)	183 ± 21.4** (-15.7%)
Day 36	365 ± 23.1	358 ± 32.2	344 ± 24.0* (-5.8%)	321 ± 27.4** (-12.1%)
Day 64	423 ± 30.6	418 ± 37.1	403 ± 31.2	380 ± 34.0** (-10.2%)

Observations/study week	Dose group (ppm)			
	Control	200	500	1500
Day 91	456 ± 32.1	448 ± 41.8	436 ± 36.0	410 ± 39.8** (-10.1%)
Mean weight gain (%)				
Days 1-8	29 ± 3.3	27 ± 4.4	28 ± 3.0	31 ± 7.6
Days 1-36	117 ± 12.2	120 ± 14.7	118 ± 9.5	133 ± 38.5* (+13.7%)
Days 1-64	151 ± 17.7	156 ± 20.5	155 ± 13.9	176 ± 51.0* (+12.8%)
Days 1-91	171 ± 19.8	175 ± 24.6	176 ± 15.4	198 ± 57.2* (+15.8%)
F1 Generation males – After mating				
Mean body weight (g)				
Day 1	470 ± 34.9	464 ± 41.1	452 ± 36.6	427 ± 39.6** (-9.5%)
Day 22	494 ± 37.0	487 ± 42.8	476 ± 40.1	448 ± 41.7** (-9.3%)
Day 37	512 ± 46.2	498 ± 48.2	480 ± 26.1	492 ± 32.8
Mean weight gain (%)				
Days 1-37	9 ± 1.8	8 ± 1.7	7 ± 2.0	8 ± 1.1
F1 Generation females - pre-mating				
Mean body weight (g)				
Day 1	137 ±12.7	131 ± 9.7	133 ± 8.0	119 ± 17.2** (-13.2%)
Day 8	158 ± 12.6	152 ± 10.8	154 ± 9.1	140 ± 14.6** (-11.4%)
Day 36	217 ± 16.8	212 ± 15.5	210 ± 16.7	197 ± 17.0** (-9.2%)
Day 64	245 ± 18.3	240 ± 17.9	235 ± 20.4	223 ± 19.9** (-9.0%)
Day 91	263 ± 18.7	256 ± 20.1	255 ± 21.0	240 ± 21.0** (-8.6%)
Mean weight gain (%)				
Days 1-8	15 ± 4.4	16 ± 3.4	16 ± 3.5	19 ± 10.7
Days 1-36	59 ± 10.8	62 ± 10.0	58 ± 10.1	70 ± 32.0
Days 1-64	79 ± 13.1	83 ± 13.8	78 ± 12.7	93 ± 39.6
Days 1-91	93 ± 14.5	96 ± 15.6	92 ± 12.8	107 ± 42.9
F1 Generation females – gestation period				
Mean body weight (g)				
Day 7	279 ± 20.7	273 ± 20.1	274 ± 20.6	258 ± 22.5** (-7.5%)
Day 14	305 ± 23.0	298 ± 21.5	299 ± 20.8	278 ± 24.3** (-8.9%)
Day 21	373 ± 28.8	368 ± 31.4	372 ± 28.8	349 ± 30.2* (-6.5%)
Mean weight gain (%)				
Day 1-21	42 ± 5.9	45 ± 9.7	48 ± 8.5*	46 ± 4.6
F1 Generation females – lactation period				
Mean body weight (g)				
Day 4	298 ± 23.3	293 ± 21.9	294 ± 16.6	277 ± 26.2** (-7.1%)
Day 7	306 ± 20.6	298 ± 19.4	298 ± 20.8	282 ± 25.4** (-7.9%)
Day 14	315 ± 22.2	309 ±22.0	315 ± 19.9	298 ± 26.1* (-5.7%)
Day 21	307 ± 19.7	297 ± 19.3	305 ± 19.0	293 ± 21.8* (-4.6%)
Mean weight gain (%)				

Observations/study week	Dose group (ppm)			
	Control	200	500	1500
Day 1-21	9 ± 6.5	9 ± 7.2	13 ± 5.3	14 ± 6.2* (+5.6%)

[a] Data obtained from pages 315 to 324 in the study report.
* Statistically different from control, p<0.05.
** Statistically different from control, p<0.01.

3. **Test substance intake:** Based on food consumption and body weight, the doses expressed as mean daily mg test substance/kg body weight during the 10 week pre-mating period are presented in Table 5. The values for the P generation are considered to be representative of the test substance intake for the entire study.

TABLE 5. Mean test substance intake during premating (mg/kg body weight/day) [a]

	Male			Female		
	200 ppm	500 ppm	1500 ppm	200 ppm	500 ppm	1500 ppm
P	12.6	32.1	95.2	14.7	35.5	106.3
F1	14.1	36.6	113.3	16.1	41.3	125.7

[a] Data obtained from pages 195-199 and 332-336 in the study report.

4. **Reproductive function:**

   a. **Estrous cycle length and periodicity:** The estrous cycles for the P and F1 groups were both comparable among controls and no treatment-related effects were identified.

   b. **Sperm measures:** No treatment-related effects were identified on sperm measures (motility, morphology, or sperm count) in the P or F1 generations.

5. **Reproductive performance:** Results for the parental animals are summarized from the report in Table 6. No significant differences on reproductive performance were observed in the P or F1 generation.

TABLE 6. Reproductive performance [a]

Observation	Dose group (ppm)			
	Control	200	500	1500
P Generation				
Mean pre-coital interval (days) – first mating	2.1	3	3	2.8
Mean pre-coital interval (days) – second mating	-	-	-	2.0
Females				
Number mated	24	24	24	24
Number pregnant	23	20	22	23
Number of Litters	23	20	22	22[b]
Fertility Index (%)	95.8	83.3	91.7	95.8
Conception Index (%)	95.8	83.3	91.7	95.8
Gestation Index (%)	100.0	100.0	100.0	95.7
Mean +s.d. gestation interval (days)	21.4 ± 0.5	21.6 ± 0.51	21.5 ± 0.51	21.5 ± 0.60
F1 Generation				
Mean pre-coital interval (days) – first mating	2.8	2.7	2.8	2.5
Mean pre-coital interval (days) – second mating	-	-	3.0	-
Females				

Observation	Dose group (ppm)			
	Control	200	500	1500
Number mated	24	24	24	24
Number pregnant	22	24	24	24
Number of Litters	22	24	24	24
Fertility Index (%)	91.7	100	100	100
Conception Index (%)	91.7	100	100	100
Gestation Index (%)	100	95.8	100	100
Mean +s.d. gestation interval (days)	21.8 ± 0.53	21.4 ± 0.58	21.5 ± 0.51	21.5 ± 0.51

[a] Data obtained from pages 204-206 and 342-344 in the study report.
[b] One female in the high dose group did not deliver any pups; and had only 2 implantation sites.
* Statistically different from control, $p<0.05$.
** Statistically different from control, $p<0.01$.

6. Parental postmortem results:

a. Organ weights: In male rats, significant increases in absolute (up to 13.95%) and relative (up to 22.11%) liver weights were observed in the mid- and high-dose groups. These effects were considered to be adverse as they occurred at doses consistent with those producing tumors in long-term studies.

b. Pathology:

1. **Macroscopic examination:** No treatment-related macroscopic findings were observed for either sex in the P generation. In F1 females, enlarged livers were considered to be treatment-related at the high dose..

2. **Microscopic examination:** Hepatocellular hypertrophy was observed in the high-dose groups of both sexes in the P and F1 parental generations. Hepatocellular hypertrophy is consistent with the observed increased liver weights. Increases in hepatocellular hypertrophy were considered to be adverse as they were observed at doses that also resulted in an increase in liver tumors.

B. OFFSPRING:

1. Viability and clinical signs: No treatment-related differences in pup viability were observed in pups from any dose level in either generation when compared to controls. No treatment related clinical signs were reported during lactation for the F1 or F2 generation.

Mean litter size and viability (survival) results from pups during lactation are summarized from the report in Table 7.

TABLE 7. Litter parameters for F_1 and F_2 generations [a]

Observation	Dose group (ppm)			
	Control	LDT	MDT	HDT
F_1 Generation				
Mean implantation sites	13.2 ± 2.85	13.5 ± 2.31	13.5 ± 1.90	12.6 ± 2.65
Number born live	281	241	258	253
Number born dead	0	1	5	0

Observation	Dose group (ppm)			
	Control	LDT	MDT	HDT
Sex ratio day 0 (M/F %)	52/48	51/49	50/50	51/49
Deaths days 0-4	4	8	4	2
Deaths days 5-21	1	0	0	2
Mean litter size Day				
Day 0	12.2 ± 3.15	12.1 ± 2.72	11.7 ± 2.21	11.5 ± 2.69
Day 4	7.7 ± 0.75	7.9 ± 0.67	7.8 ± 0.85	7.7 ± 0.89
Day 21	7.7 ± 0.82	7.9 ± 0.67	7.8 ± 0.85	7.6 ± 0.91
Birth index	92.7	89.3	87.2	91.0
Viability Index	98.6	96.7	98.4	99.2
Weaning Index	99.4	100	100	98.8
F_2 Generation				
Mean implantation sites	12.8 ± 2.27	12.9 ± 3.19	13.7 ± 2.56	13.5 ± 2.15
Number born live	248	275	295	291
Number born dead	2	3	0	2
Sex ratio day 0 (M/F %)	45/55	49/51	49/51	49/51
Deaths days 0-4	1	3	4	2
Deaths days 5-21	0	0	3	0
Mean litter size				
Day 0	11.3 ± 2.55	11.5 ± 3.75	12.3 ± 2.76	12.1 ± 2.29
Day 4	7.9 ± 0.64	7.5 ± 1.69	7.8 ± 0.64	8.0 ± 0.00
Day 21	7.9 ± 0.64	7.5 ± 1.69	7.7 ± 0.69	8.0 ± 0.00
Birth index	88.3	88.7	89.7	89.8
Viability Index	99.6	98.9	98.6	99.3
Weaning Index	100	100	100	100

[a] Data obtained from pages 204-207 and 342-345 in the study report.
* Statistically different from control, $p<0.05$
** Statistically different from control, $p<0.01$

2. **<u>Body weight</u>:** In the F1 and F2 generations, significant decreases in body weight were observed on lactation day (LD) 21 in high-dose groups in both males and females. Significant decreases in pup body weights at low-dose in the F2 generation were not considered to be treatment related as no dose-response occurred, no evidence of decreased pup weights occurred at the low dose in the F1 generation, and low-dose body weight were decreased on lactation day 1 with minimal progression of toxicity on lactation day 21. Additionally, the decrease body weights at 500 ppm in both the F1 and F2 generations were not considered to be adverse. The observed decreases in body weight were marginal (5-7%), at PND 21 detoxification enzymes in pups are expected to be similar to those of adult rats, body weights were fully recovered in F1 pups selected for mating by pre-mating day 0, the decreases primarily occurred between PND 14 and PND 21 which may result for being "double-dosed" from exposure to momfluorothrin in the milk and in the feed, and be a result of overexposure.

   Selected mean pup body weight data are presented in Table 8.

TABLE 8. Mean (±SD) Litter and pup weights (g) [a]

Lactation day	Dose group (ppm)							
	0	200	500	1500	0	200	500	1500
	F_1 Pups – male				F_2 Pups – male			
1	6.3 ± 0.67	6.4 ± 0.66	6.4 ± 0.57	6.4 ± 0.55	6.6 ± 0.61	6.2 ± 0.75	6.5 ± 0.66	6.4 ± 0.56
4	9.3 ± 1.41	9.8 ± 1.43	9.8 ± 0.92	9.8 ± 1.28	10.4 ± 1.32	9.5 ± 1.51	10.0 ± 1.42	10.0 ± 1.23
7	15.5 ± 1.85	16.0 ± 1.70	15.8 ± 1.08	15.8 ± 1.61	17.1± 1.92	15.7 ± 1.60*	16.4 ± 1.66	16.1 ± 1.65
14	32.8 ± 2.66	33.0 ± 2.86	32.4 ± 1.63	31.9 ± 2.56	35.1 ± 2.75	33.3 ± 2.44	34.6 ± 2.24	32.5 ± 2.75** (-7.41%)
21	52.4 ± 4.08	51.6 ± 4.59	48.8 ± 3.30** (-6.9%)	46.0 ± 3.86** (-12.2%)	56.0 ± 5.31	51.4 ± 4.66** (-8.2%)	52.0 ± 3.47** (-7.2%)	47.2 ± 3.75** (-15.72)
	F_1 Pups – female				F_2 Pups – female			
1	5.9 ± 0.65	6.2 ± 0.71	6.1 ± 0.55	6.2 ± 0.61	6.3 ± 0.65	5.9 ± 0.71	6.2 ± 1.65	6.2 ± 0.63
4	9.9 ± 1.37	9.4 ± 1.48	9.4 ± 1.05	9.5 ± 1.46	10.2 ± 1.28	9.0 ± 1.49*	9.6 ± 1.46	9.7 ± 1.23
7	15.1 ± 1.69	15.4 ± 1.81	15.2 ± 1.53	15.3 ± 1.72	16.8 ± 1.66	14.9 ± 1.78**	15.8 ± 1.86	15.7 ± 1.52
14	32.1 ± 2.47	32.1 ± 2.98	31.5 ± 1.76	31.1 ± 2.39	34.5 ± 2.46	31.7 ± 2.94**	33.8 ± 2.21	32.0 ± 2.72** (-7.25%)
21	50.8 ± 3.49	49.7 ± 4.46	47.3 ± 3.29** (-6.9%)	44.3 ± 3.51** (-12.8%)	54.3 ± 4.40	49.1 ± 4.00** (-9.6%)	51.3 ± 3.18** (-5.5%)	45.6 ± 3.62** (-16%)

[a] Data obtained from 244-245 and 376-377 in the study report.
*Statistically different from control, $p<0.05$
**Statistically different from control, $p<0.01$

3. **<u>Sexual maturation</u> (F_1):** Time to sexual maturation was slightly delayed (≈ 3 days) in high-dose females occurring in the absence of significant body weight decreases.

TABLE 9. Sexual maturation summary of F1 pups [a]

Dose group (ppm)				
	0	**200**	**500**	**1500**
	F_1 Pups – male			
Day p.p	25.0 ± 0.0	25.1 ± 0.3	25.2 ± 0.6	26.3 ± 1.0+
Weight (g)	68.58 ± 3.89	67.30 ± 6.75	65.07 ± 6.37	60.20 ± 7.06**
	F_1 Pups – female			
Day p.p	34.1 ± 1.7	34.7 ± 1.9	34.3 ± 1.4	37.0 ± 3.0+ (+8.5%)
Weight (g)	112.52 ± 10.56	110.70 ± 11.89	111.76 ± 8.30	108.52 ± 11.37

[a] Data obtained from 248 and 249 in the study report.
*Statistically different from control, $p<0.05$
**Statistically different from control, $p<0.01$
+ Statistically different from control, $p<0.05$ using Steel-test

4. Offspring postmortem results:

a. Organ weights: Spleen weights were significantly decreased in the mid- and high-dose males of the F1 generation and females of the F1 and F2 generations. Decreases in absolute thymus weights in the high-dose of all groups were considered to be the result of decreased body weights as significant differences in relative organ weights were not observed. The decreased spleen weights were not considered to be adverse as they were only slightly outside of historical control ranges, the effects fully recovered in the F1 adults, no gross lesions or macroscopic observations were identified at any dose in either sex, no effects on the spleen were observed throughout the momfluorothrin database, and no immunotoxic effects were identified following the immunotoxicity assay in rats.

Table 10: Select organ weights in offspring.

	Dose group (ppm)			
	0	**200**	**500**	**1500**
	F_1 Pups – male			
Body W.	51.5 ± 3.8	50.5 ± 4.2	48.8 ± 3.6	44.9 ± 4.5**
Thymus				
Abs.	0.200 ± 0.034	0.206 ± 0.039	0.186 ± 0.023	1.46 ± 0.05*
Rel.	0.388 ± 0.065	0.407 ± 0.063	0.382 ± 0.041	0.384 ± 0.054
Spleen				
Abs.	0.26 ± 0.04	0.24 ± 0.04	0.21 ± 0.05** (-19.24%)	0.19 ± 0.05** (-26.93%)
Rel.	0.50 ± 0.06	0.47 ± 0.06	0.42 ± 0.09** (-16%)	0.42 ± 0.07** (-16%)
	F_2 Pups – male			
Body W.	55.5 ± 4.3	50.9 ± 4.9**	52.0 ± 3.8*	47.3 ± 3.9**
Thymus				
Abs.	0.219 ± 0.035	0.200 ± 0.038	0.202 ± 0.038	0.184 ± 0.031**
Rel.	0.397 ± 0.69	0.393 ± 0.059	0.387 ± 0.058	0.389 ± 0.053
Spleen				
Abs.	0.27 ± 0.04	0.25 ± 0.05	0.24 ± 0.04	0.22 ± 0.04**
Rel.	0.49 ± 0.05	0.48 ± 0.05	0.47 ± 0.06	0.46 ± 0.07
	F_1 Pups – female			
Body W.	48.8 ± 3.8	48.4 ± 5.0	46.1 ± 3.9	44.1 ± 4.0**
Thymus				
Abs.	0.203 ± 0.030	0.208 ± 0.042	0.190 ± .0.41	0.174 ± 0.034*
Rel.	0.415 ± 0.051	0.428 ± 0.073	0.411 ± 0.072	0.394 ± 0.059
Spleen				
Abs.	0.25 ± 0.05	0.25 ± 0.05	0.20 ± 0.04** (-20%)	0.19 ± 0.03** (-24%)
Rel.	0.51 ± 0.09	0.51 ± 0.08	0.43 ± 0.08** (-15.69%)	0.43 ± 0.06** (15.69%)
	F_2 Pups – female			
Body W.	52.9 ± 4.5	48.7 ± 3.7**	50.1 ± 3.2*	45.2 ± 3.5**
Thymus				
Abs.	0.224 ± 0.033	0.210 ± 0.040	0.199 ± 0.036	0.178 ± 0.025**
Rel.	0.424 ± 0.64	0.429 ± 0.062	0.397 ± 0.065	0.393 ± 0.048
Spleen				
Abs.	0.28 ± 0.06	0.25 ± 0.05	0.23 ± 0.04** (-17.86%)	0.21± 0.04** (-25%)
Rel.	0.52 ± 0.82	0.51 ± 0.08	0.47 ± 0.07* (-9.62%)	0.46 ± 0.08* (-11.54%)

[a] Data obtained from 250-255 and 380-385 in the study report.
*Statistically different from control, $p<0.05$
**Statistically different from control, $p<0.01$

b. Pathology:

1. **Macroscopic examination:** No treatment related macroscopic findings were reported for the either the F1 or F2 generation pups.

2) **Microscopic examination:** Histopathological examination was not conducted. No differences in sperm or ovary staging were reported between the controls and high-dose group for either generation.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: A No-Observed-Adverse-Effect Level (NOAEL) for general effects in P and F1 generation parents was established at the dietary level of 200

ppm, based on impaired body weight development, occurrence of increased liver weights and corresponding histological findings that were considered to be of metabolic adaptive character and therefore non-adverse. A NOAEL for general effects in F1 and F2 pups was established at 200 ppm, based on impaired body weight development and occurrence of decreased spleen weights. A NOAEL for reproductive effects was established at 500 ppm, based on delayed sexual maturation in F1 offspring that, however, reflected the smaller body weights.

B. REVIEWER COMMENTS: Significant body weight decreases were observed in the parents of the F1 generation at the high-dose. Additionally, increases in hepatocellular hypertrophy were considered to be adverse as they were observed at doses that also resulted in an increase in liver tumors in the long-term studies. Therefore, the LOAEL and NOAEL for parental animals is 1500 and 500 ppm.

The reproductive LOAEL is 1500 ppm based on increased sexual maturation time in females. Delayed maturation in females was considered by the reviewer to be treatment-related and adverse as a delay of greater than 3 days is biologically significant and may not be fully explained by body weight decrements. The NOAEL is 500 ppm.

The offspring LOAEL is 1500 ppm based on decreases in pup body weights in the F1 and F2 generation of both sexes. The NOAEL is 500 ppm.

C. STUDY DEFICIENCIES: None